Fine-Needle Aspiration Cytology for the Diagnosis of Metastatic Melanoma

Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To perform a thorough review and meta-analysis of studies that have shown non–image-guided fine-needle aspiration cytology (FNAC) to be highly sensitive and specific for assessing questionable metastatic melanoma to lymph nodes.

Methods: MEDLINE and Scopus were searched for potentially relevant articles with a search string including the words “melanoma” and “fine needle.” All relevant articles were screened by two authors (B.J.H. and R.L.S.). Full articles were screened for extractable data, and the data was pooled for analysis.

Results: Of 978 unique studies found, 10 (5,518 cases) met our inclusion criteria. In a pooled analysis of palpation and ultrasound-guided fine-needle aspirations, the area under the receiver operating characteristic curve was 0.99 (95% confidence interval [CI], 0.99-1.00). The summary estimates for the sensitivity and specificity were 0.97 (95% CI, 0.95-0.98) and 0.98 (95% CI, 0.98-1.00), respectively.

Conclusions: With a sensitivity and specificity of 0.97 and 0.99, the overall diagnostic accuracy of FNAC for metastatic melanoma is quite high, and with a positive and negative likelihood ratio of 58 and 0.03, FNAC for metastatic melanoma should be the first-line option in a patient with a clinically suspected mass and a history of melanoma.

Upon completion of this activity you will be able to:
• cite the overall sensitivity and specificity of fine-needle aspiration cytology (FNAC) for metastatic melanoma.
• describe anatomic sites or clinical scenarios where there is an increased risk for false-negative and false-positive diagnoses of metastatic melanoma with FNAC.
• list areas that still need to be further researched in FNAC for metastatic melanoma and discuss ways to improve reporting in future articles.
• describe clinical scenarios in which palpation-guided FNA or ultrasound-guided FNA is preferred.
• synthesize a clinical algorithm to properly facilitate the care of a patient with a history of melanoma and with a negative or positive FNA of a suspicious nodule.

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Melanoma of the skin now represents the eighth most common primary cancer type among men and women in the United States,1 and the incidence among non-Hispanic white men and women steadily increased from 1992 through 2006.2 Although melanoma accounts for less than 5% of all skin cancers,3 it is the cause of the greatest number of skin cancer–related deaths worldwide.3 Some studies have even indicated that rates of melanoma have been doubling or tripling over 10- to 30-year periods.4,5 Although the direct cause for this is unknown, some speculate it is due to a true increase, while others postulate that it is due to earlier detection of thinner, more prognostically favorable melanomas.6,7 However, one...
recent study indicates that thin melanomas (Breslow depth ≤1 mm) may account for approximately 30% of melanoma-related deaths.2 Regardless of the actual cause for this increase in incidence, the most obvious result of the rising number of patients with a diagnosis of melanoma is increased clinical follow-up in these patients for the evaluation of new suspicious lesions and surveillance by dermatologists and oncologists for evidence of possible metastatic spread.

Although fine-needle aspiration cytology (FNAC) has limited usefulness in the diagnosis of primary melanocytic lesions of the skin (except for unusual clinical locations, such as oral mucosa8 or intraocular lesions9) because of the clinical ease of punch biopsy, shave biopsy, or wedge resection,10 FNAC is a useful diagnostic procedure for clinically suspicious lesions in patients with a previous diagnosis of melanoma. It is a common procedure that can be done in the clinic using simple palpation for more superficial lesions or with the assistance of image guidance for more deeply seated lesions. It also helps avoid general anesthesia, a short hospital stay, and other associated costs of general surgery.

Numerous studies have shown that use of FNAC for assessing questionable metastatic melanoma to lymph nodes without image guidance is highly sensitive and specific.11-13 One study14 demonstrated that ultrasound-guided FNAC for suspected lymph node metastases was highly sensitive and specific, and several other studies have shown that in addition to lymph nodes, soft tissue, and skin, FNAC can be performed with good results, with15-17 or without image guidance,18-21 in other sites such as the liver, lung, adrenal glands, kidney, pancreas, parotid gland, mandibular gland, omentum, spine, and thyroid gland. FNAC is commonly used at many institutions in the United States as well as abroad. However, clinicians may be reluctant to use FNAC as a diagnostic tool due to the concern about the detrimental impact to the patient if a false-negative or false-positive result is received. Because the literature on the accuracy of FNAC for metastatic melanoma has not been adequately summarized, we performed a systematic review and meta-analysis to summarize the diagnostic accuracy of FNAC for metastatic melanoma.

Materials and Methods

Literature Search

We followed guidelines for systematic reviews of diagnostic accuracy studies.22-24 We searched MEDLINE and Scopus on June 17, 2012, using the following search string: melanoma AND fine needle. There was no restriction on language, period, or study design.

The titles and abstracts were independently screened by two authors (B.J.H. and R.L.S.). Studies were included if they contained data on the accuracy of fine-needle aspiration (FNA) for the diagnosis of metastatic melanoma. Studies using either image-guided or palpation-guided FNA were eligible for inclusion. Discrepancies were resolved by discussion.

A citation search (“forward search”) and reference search (“backward search”) were conducted using Scopus on June 23, 2012. Duplicates were removed, and the titles and abstracts of these additional studies were screened for potentially relevant studies. Full-text articles were then obtained for all potentially relevant studies.

Data Extraction

The full texts of all potentially relevant articles were independently evaluated by two authors (B.J.H. and R.L.S.). Studies were included if they contained extractable data on either histologically or clinically verified cases of lesions suspicious for recurrent melanoma and if the results could be extracted in the form of true positives, false positives, false negatives, and true negatives. We did not extract information regarding histologic subtypes of melanoma in this study. Data from foreign-language articles (non-English) were extracted by pathologists with knowledge of the language. Inadequate or indeterminate biopsy specimen results were not counted in the calculation of accuracy. FNAC diagnoses of “suspicious for malignancy” or “atypical” were counted as malignant. When results of a study were published more than once, we included only the most complete data.

Quality Assessment

Risk of bias and applicability of all included studies was assessed using the QUADAS-2 (University of Bristol, Bristol, England) instrument.25 Assessments were conducted independently by two authors (B.J.H. and R.L.S.).

Statistical Analysis

Summary receiver operating characteristic curves (SROCs) were developed using the hierarchical method. Computations were performed using the metandi and midas routines in Stata 12 (StataCorp, College Station, TX).

Results

Literature Search

A flow diagram of the literature search is presented in Figure I. The initial search identified 978 unique studies from which 41 eligible articles were obtained that appeared to contain extractable data on more than one case of FNA for metastatic melanoma. Since our search string (melanoma AND fine needle) was quite broad, numerous studies (n =
937) were case reports, summaries, or editorials or were not performed for metastatic melanoma. Of the 41 eligible articles that did possibly contain extractable data and were thoroughly reviewed by both authors (B.J.H. and R.L.S.), only 10 studies (5518 cases) met our inclusion criteria (extractable data in the form of true positives, false positives, false negatives, and true negatives).

**Characteristics of Included Studies**

The key features of the included studies are presented in Table 1.11,12,14-21 All studies were performed at a university medical center, and none were performed in a community setting. The publication rate increased during the period, with half of the studies published in the past eight years. All studies were retrospective. Six of the 10 studies reported who aspirated the specimens, with all indicating that the operator had significant experience with the procedure. Four studies did not describe who obtained the sample, four studies specified that samples were obtained by a cytopathologist, one study indicated that specimens were obtained by a radiologist, and one study determined that cytopathologists tested for palpable lesions and radiologists performed image-guided tests for lesions. Approximately two-thirds of the studies reported summary statistics on age and sex distributions of patients, and all those reportings were similar. No studies were blinded.

A total of 285 nondiagnostic cases were reported, accounting for 5.2% of the total, and they were excluded from the analysis. Twenty-three other cases were excluded from one study19 because there was no histologic or clinical follow-up available.

In addition, several articles also classified lesions as “atypical,” “suspicious,” or “questionably malignant,” which accounted for 113 (2.05%) of cases. In our analysis, these lesions were reclassified as malignant because they clinically would most likely have been treated that way. However, we also performed a second analysis that reclassified all lesions as benign. Also, there were 10 cases in which a diagnosis of melanoma was made on FNA that, on final histology, turned out to be a different malignancy. These were classified as false positive since we were evaluating sensitivity and specificity of a cytodiagnosis of melanoma. Some articles, however, stated that a few cases did turn out to be a different malignancy but did not specify the number, and most classified these cases as true positives since a diagnosis of malignancy was made correctly. Atypical, suspicious, questionably malignant, and other malignant diagnoses in each article are summarized in Table 2.11,12,14-21

**Table 1**

Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Guidance</th>
<th>Blinded</th>
<th>Study Design</th>
<th>Aspirator</th>
<th>Site</th>
<th>% LN</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
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<td>None</td>
<td>No</td>
<td>Retro</td>
<td>NA</td>
<td>LN</td>
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<td>No</td>
<td>Retro</td>
<td>Cytopathologist</td>
<td>LN</td>
<td>100</td>
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</tr>
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<td>US guided</td>
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<td>Retro</td>
<td>Radiologist</td>
<td>LN</td>
<td>100</td>
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<tr>
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<td>No</td>
<td>Retro</td>
<td>Cytopathologist</td>
<td>Variable</td>
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<td>Retro</td>
<td>Cytopathologist and radiologist</td>
<td>Variable</td>
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<td>Variable</td>
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<td>Rodrigues et al19</td>
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<td>Cytopathologist</td>
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<tr>
<td>Schoengen et al17</td>
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<td>Retro</td>
<td>Cytopathologist</td>
<td>Variable</td>
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<td>Germany</td>
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<tr>
<td>Voit et al10</td>
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<td>No</td>
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<td>NA</td>
<td>Variable</td>
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<tr>
<td>Zeelen et al20</td>
<td>None</td>
<td>No</td>
<td>Retro</td>
<td>NA</td>
<td>Variable</td>
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<td>Germany</td>
</tr>
</tbody>
</table>

LN, lymph node; NA, not applicable/unknown; Retro, retrospective; US, ultrasound.

* All studies were performed at a university hospital setting.
Diagnostic Accuracy

The extracted accuracy data are presented in Table 2. The SROC curve for positive vs negative lesions is shown in Figure 2. A forest plot is presented in Figure 3. In a pooled analysis of both palpation and ultrasound-guided FNAs, the area under the receiver operating characteristic curve was 0.99 (95% confidence interval [CI], 0.99-1.00). The summary estimates for the sensitivity and specificity were 0.97 (95% CI, 0.95-0.98) and 0.98 (95% CI, 0.98-1.00), respectively. The positive likelihood ratio was 58 (95% CI, 23-139), and the negative likelihood ratio was 0.03 (95% CI, 0.01-0.05). There was no significant heterogeneity among studies (P < .001).

Meta-regression found no difference in accuracy between palpation-guided and ultrasound-guided FNA (P = .75).

We conducted a sensitivity analysis to assess the impact of classifying atypical lesions as malignant. In this analysis, we reclassified atypical cases as benign. The accuracy estimates showed no significant change as a result of this reclassification.

Quality Appraisal

The quality appraisal of the included studies is presented in Table 3.11,12,14-21 There were no concerns of applicability. All studies included consecutive patients and applied no exclusion criteria. All but two studies followed all patients. Two studies had partial verification bias because they included only patients with histologic follow-up. Sensitivity analysis showed that these studies had no impact on the results.

Discussion

To our knowledge, our study is the first to summarize the data regarding accuracy of FNA for the diagnosis of metastatic melanoma and provide possible areas of improvement for future studies.

With a sensitivity and specificity of 0.97 and 0.99, the overall diagnostic accuracy of FNAC for metastatic melanoma is high. Given the positive and negative likelihood ratios of 58 and 0.03, FNAC should be the first-line diagnostic option in patients with a mass clinically suspicious for metastatic melanoma. Choice of FNAC in this setting is recommended...

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusive Diagnoses</th>
<th>Atypical</th>
<th>Suspicious</th>
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<td></td>
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<td>FP</td>
<td>FN</td>
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<td>1</td>
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<tr>
<td>Hafström et al18</td>
<td>48</td>
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<td>3</td>
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<tr>
<td>Murali et al15</td>
<td>780</td>
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<td>30</td>
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<tr>
<td>Perry et al21</td>
<td>63</td>
<td>0</td>
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<tr>
<td>Rodrigues et al19</td>
<td>160</td>
<td>3</td>
<td>25</td>
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<tr>
<td>Schoengen et al17</td>
<td>85</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Voit et al16</td>
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<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Zeelen et al20,21</td>
<td>319</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

FN, false negative; FP, false positive; ND, nondiagnostic; TN, true negative; TP, true positive.

* Does not include diagnoses of atypical, suspicious, or nondiagnostic diagnoses.

1 Includes two diagnoses positive for malignancy but not melanoma.
2 No final diagnosis provided.
3 Thirteen benign and 10 malignant diagnoses without follow-up were excluded.
because of its low procedural cost, minimal risk of harm to the patient, and rapid turnaround time. The short time between performance of FNAC and the availability of diagnosis allows rapid delivery of information to the patient and expedites clinical decisions and the initiation of appropriate therapy.

Our analysis revealed important characteristics of FNAC in the workup of recurrent or metastatic malignant melanoma. Clinicians considering the use of FNAC for the workup of pulmonary nodules in patients with a history of malignant melanoma should remember that most of these patients have metastatic disease, and the pulmonary nodules are metastatic deposits. Hence, negative results often indicate inadequate sampling of the lesion. In addition, pulmonary FNAs are often of low cellularity, containing only scattered malignant cells. Subcutaneous nodules likewise often represent metastatic disease and often show a spindled or variant morphology. Isolated lymphadenopathy in patients with a history of malignant melanoma is often reactive in nature and does not represent metastatic disease. However, when malignant melanoma cells are encountered in these enlarged lymph nodes, the morphology is often typical for melanoma. Site of lymphadenopathy is also important in analyzing results of FNAC. False-negative results occur more frequently in axillary lymph node aspirates. This increased likelihood of

Figure 3. Forest plot of included studies. Each study is represented by a box and whisker. The box represents the estimate for sensitivity or specificity. The whisker represents the 95% confidence interval. The vertical line represents the pooled estimate for sensitivity and specificity. The width of the diamond represents the 95% confidence interval for the pooled estimate.

Table 3. Quality Assessment of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Selection</td>
<td>Index Test</td>
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<tr>
<td>Basler et al 11</td>
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<td>Cangiarella et al 12</td>
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</tr>
<tr>
<td>Dalle et al 14</td>
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<td>Hafström et al 18</td>
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<td>Perry et al 21</td>
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<tr>
<td>Rodrigues et al 19</td>
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<td>Low</td>
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<tr>
<td>Schoengen et al 17</td>
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<td>Low</td>
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<tr>
<td>Voit et al 16</td>
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<td>Low</td>
</tr>
<tr>
<td>Zeelen et al 20</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Combined</td>
<td>Low</td>
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</tr>
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</table>
false-negative results can, in part, be countered by increasing the number of needle passes when lymphadenopathy occurs in an axillary location.\(^{28}\)

The available literature indicates that when FNAC is performed without the assistance of a cytopathologist or cytotechnologist (performed by the clinician on site), liquid-based preparations are more commonly used. These preparations alter the cytomorphology of the specimens available for analysis. Liquid-based preparations, in contrast to conventional smears, have reduced background melanin, blood, lymphocytes, and necrotic debris. The number of intranuclear cytoplasmic pseudoinclusions is also reduced, cell clusters are smaller, and nuclear chromatin appears coarser.\(^{29}\) The cytology of unusual histologic subtypes of melanoma also affects the appearance of cytologic preparations. Thus, cytologic findings vary from the classic morphology in examples of desmoplastic melanoma, small cell variant, myxoid melanoma, and other subtypes.

The cytopathologist needs to be cognizant of the fact that many patients with malignant melanoma also have a second malignancy.\(^{15,21}\) This complicates interpretation of cytologic preparations given the wide morphologic spectrum of melanoma, which may overlap that seen in other malignancies, including sarcomas and lymphomas. The possibility of secondary malignancy must always be considered. Paucicellular smears represent a significant diagnostic pitfall and, when combined with high clinical suspicion in a patient with a past history of melanoma, may lead to a false-positive diagnosis.\(^ {15,19}\)

In the studies, the most common cause of a false-negative result in FNAC was an inadequate specimen.\(^ {15,16,19,21}\) The most common cause of a false-positive result was a second malignancy.\(^ {15}\) Additional causes for false-negative results include obesity, difficult areas for aspiration (deep inguinal lymph nodes), superficial subcutaneous lesions associated with fibrosis or a previous scar, and small size or poor circumscription of the suspicious lesion.\(^ {16}\) In addition, enlarged lymph nodes with only small focal deposits of metastatic malignant melanoma also may result in false-negative results.\(^ {15}\) Palpation-guided vs image-guided FNA appears to increase the probability of a false-negative result.\(^ {15}\)

False-positive results may occur due to overinterpretation of reactive fibroblasts as well as benign spindle cell lesions (nodular fasciitis) and the presence of atypical histiocytes, which may mimic melanoma cells.\(^ {15}\) Strict criteria for the number of cells required for an adequate smear are not currently available, but a single study used the criterion of at least 100 cells on two different slides.\(^ {16}\) Unfortunately, in many small, superficial, or fibrotic cutaneous/subcutaneous lesions, this cut point cannot be met. The use of ultrasound has led to the investigation of smaller lymph nodes (diameters <1 cm).\(^ {16}\) Aspiration of these small lymph nodes is associated with a lower sample volume and may necessitate adequacy criteria with a smaller number of cells. Voit et al\(^ {16}\) was also the only study to specifically try to determine whether size of the lesion affects the sensitivity and specificity of FNA. In their study, diameter of the lesion (>10 or <10 mm in diameter) did have a small effect on sensitivity (99% for lesions >10 mm in diameter vs 94.6% for lesions <10 mm in diameter), but specificity remained unchanged at 100% in a study involving 738 total cases. However, of the 11 total false-negative cases misdiagnosed by FNA, four were less than 10 mm in diameter and yielded hypocellular/paucicellular specimens (three cases) or poor material (one case). This result indicates that, although ultrasound B-scan technology can detect much smaller masses, the sensitivity is decreased for lesions less than 10 mm. It should be kept in mind that paucicellular or hypocellular specimens from smaller lesions are at a higher risk for false-negative results and therefore should be followed closely with excisional biopsy or lymph node removal to ensure the correct diagnosis.

One study, which investigated the results of ultrasound-guided FNAC,\(^ {16}\) was unable to demonstrate that anatomic site (subcutaneous, organ specific, or lymph node) had a measurable effect on diagnostic sensitivity. Additional studies investigating these issues to a greater degree with larger numbers of cases are needed to properly determine if FNAC at certain sites has lower sensitivity.

A number of reports have discussed that the reliability of FNAC depends on the expertise and training of the cytopathologists.\(^ {16}\) We are unaware of any study directly comparing FNAC accuracy among residents, fellows, and attendings who have different training backgrounds and levels of experience.

An important issue in the safety of FNAC is the extent of the procedure’s risk to patients. Rare case reports of “tumor implantation” in FNAC tracks have been reported.\(^ {27,30}\) Such tumor implantation appears to be exceedingly rare, but sites of FNAC should be monitored for potential recurrence/tumor implantation. Both case reports of tumor seeding (one endoscopic ultrasound-guided FNAC\(^ {27}\) and one of an enlarged lymph node in the supraclavicular fossa\(^ {31}\)) were successfully resected. Interestingly, FNAC of ocular melanomas is associated with a significant incidence of seeding.\(^ {31,33}\) Despite the higher occurrence of tumor seeding in FNAC tracks in the orbital region, there has been only one well-documented case of actual recurrent melanoma along the biopsy track.\(^ {33}\)

Our meta-analysis demonstrated that reporting differed significantly from study to study, with some reports having very detailed information, including site, type of biopsy used, number of passes, skill/experience of the operator, experience of the pathologist reviewing the cases, and the actual operator of the FNAC (cytopathologist, radiologist, or clinician). Other reports did not even identify the site. More consistent reporting methods of studies will greatly improve our ability to determine if certain anatomic sites are more or less sensitive or specific.
In addition, these studies could help determine whether experience of the operator/reviewing pathologist or other variables, such as number of passes, affect sensitivity and specificity.

Important issues that should be addressed in future studies regarding the sensitivity and specificity for the diagnosis of malignant melanoma should include a comparison of image-guided (ultrasound vs computed tomography vs magnetic resonance imaging) techniques. Further investigation as to whether performer experience has an effect on the sensitivity or specificity should be undertaken to determine if inexperienced clinicians, pathologists, radiologists, or other medical personnel can perform adequate FNAC with an acceptable diagnostic accuracy. Although most reports state that the expertise of the cytopathologists are important, no study to date has directly compared levels of expertise with diagnostic accuracy for experienced vs inexperienced cytopathologists or radiologists. When reports did specify the experience of the cytopathologist or radiologist, they often reported only highly experienced individuals and did not specify years of training or utilization of the FNAC technique.

A final issue that requires further investigation is whether FNAC of sentinel lymph nodes has a diagnostic accuracy similar to excisional biopsy. Several studies have investigated this issue.34-36 Results in these reports have been mixed regarding sensitivity and specificity. Given current data, it appears that ultrasound-guided FNAC should not be used in place of sentinel lymph node biopsy.37,38

In our clinical practice (UT Southwestern), we use FNA biopsy as a minimally invasive method to detect melanoma metastasis in high-risk patients with concurrent or previously resected primary cutaneous melanoma who present with palpable or nonpalpable/imaging-detected regional lymphadenopathy. Figure 4. Patients with FNA biopsy-confirmed nodal metastasis from melanoma complete additional staging evaluation (e.g., positron emission tomography/computed tomography), and regional lymphadenectomy is offered to those patients who have no evidence of distant disease. An excisional lymph node biopsy should be performed when the FNA biopsy is nondiagnostic or atypical cells are detected on histopathology without being able to secure a diagnosis of melanoma. Further management of the patient is then directed by the histopathology results from this excisional biopsy. When no malignancy is detected within the regional lymph nodes, the primary cutaneous melanoma is excised (with or without sentinel lymph node biopsy) or ongoing surveillance continued.

In conclusion, we found that FNAC is a highly accurate technique for the diagnosis of metastatic melanoma. The estimated sensitivity is 0.97 and the specificity is 0.98.

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References


